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(54) **Title: ACE-2 INHIBITING COMPOUNDS AND METHODS OF USE THEREOF**
(54) **Titre: COMPOSES INHIBANT ACE-2 ET LEURS PROCEDES D'UTILISATION**

(57) Abstract

ACE-2 inhibiting compounds are disclosed. Methods of using the compounds and pharmaceutical compositions containing the compounds are also claimed.

(57) Abrégé

L'invention concerne des composés inhibant ACE-2 ainsi que des procédés d'utilisation de compositions pharmaceutiques contenant lesdits composés.

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(71) Applicant: MILLENNIUM PHARMACEUTICALS, INC. [US/US]; 75 Sidney Street, Cambridge, MA 02139 (US).

(72) Inventors: ACTON, Susan, L.; 42 Munroe Road, Lexington, MA 02421 (US). OCAIN, Timothy, D.; 45 Indian Head Road, Framingham, MA 01701 (US). GOULD, Alexandra, E.; 23 R. Fairmont Street, Cambridge, MA 02139 (US). DALES, Natalie, A.; 26 Fisher Road, Arlington, MA 02476 (US). GUAN, Bing; 27 Shepard Street, Brighton, MA 02435 (US). BROWN, James, A.; 1099 Edgell Road, Framingham, MA 01701 (US).

(74) Agents: HANLEY, Elizabeth, A.; Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109 (US) et al.

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(54) Title: ACE–2 INHIBITING COMPOUNDS AND METHODS OF USE THEREOF

(57) Abstract

ACE–2 inhibiting compounds are disclosed. Methods of using the compounds and pharmaceutical compositions containing the compounds are also claimed.

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ACE-2 INHIBITING COMPOUNDS AND METHODS OF USE THEREOF

Background of the Invention:

Hypertension, or high blood pressure, is the most common disease affecting the heart and blood vessels. Statistics indicate that hypertension occurs in more than 50 million Americans. The prevalence of hypertension increases with age. Between 85 and 90% of cases are primary (i.e., essential) hypertension, i.e., a persistently elevated blood pressure that cannot be attributed to any particular organic cause. The remaining percentage of cases are secondary hypertension, i.e., elevated blood pressure having an identifiable underlying cause such as kidney disease and adrenal hypersecretion.

Hypertension is of considerable concern because of the harm it can do to the heart, brain, and kidneys if it remains uncontrolled. The heart is most commonly affected by high blood pressure. When blood pressure is high, the heart uses more energy in pumping against the increased resistance caused by the elevated arterial blood pressure. Because of the increased effort, the heart muscle thickens and the heart becomes enlarged and needs more oxygen. If it cannot meet the demands put on it, angina pectoris or even myocardial infarction may develop. Hypertension can result in numerous complications including left ventricular failure; atherosclerotic heart disease; retinal hemorrhage, exudates, papilledema, and vascular accidents; cerebrovascular insufficiency with or without stroke; and renal failure. An untreated hypertensive patient is at great risk of developing disabling or fatal left ventricular failure, myocardial infarction, cerebral hemorrhage or infarction, or renal failure at an early age. Hypertension is the most important risk factor predisposing to stroke and is an important risk factor predisposing to coronary atherosclerosis.

An abnormal blood pressure can also result from specific conditions or diseases, such as heart failure. Heart failure is a chronic or acute state that results when the heart is not capable of providing sufficient cardiac output to satisfy the metabolic needs of the body. Heart failure is commonly referred to as congestive heart failure (CHF), since symptoms of increased venous pressure (pulmonary congestion with left heart failure and peripheral edema with right heart failure) are often predominant. Symptoms and signs of CHF include fatigue, peripheral and pulmonary edema, and visceral congestion (e.g., dyspnea). These symptoms are produced by diminished blood flow to the various

tissues of the body and by accumulation of excess blood in the various organs, that results from the heart being incapable of pumping out the blood. Heart failure can result from several underlying diseases, most commonly in industrialized nations from atherosclerotic coronary artery disease with myocardial infarction. Myocardidis, various cardiomyopathies, and valvular and congenital defects may also result in heart failure (Anderoli et al., Cecil: Essentials of Medicine, Third Edition, WB Saunders Company, 1993). A major problem in CHF is the inability of the failing left ventricle to maintain a normal blood pressure, thus resulting in increased pre- and afterload, and leading to progressive ventricular dilation with wall remodeling. Vasodilators which induce a reduction in pre- and afterload, i.e., reduction of the systemic vascular resistance and reduction of the peripheral vascular resistance, respectively, are currently used to treat CHF (Lionel H. Opie, Drugs for the Heart, Third Edition, WB Saunders Company, 1991).

One important system involved in regulating blood pressure is the renin-angiotensin-aldosterone system. In this system, renin, a proteolytic enzyme formed in the granules of the juxtaglomerular apparatus cells catalyzes the conversion of angiotensinogen (a plasma protein) into angiotensin I, a decapeptide. This inactive product is then cleaved by a converting enzyme, termed angiotensin converting enzyme (ACE) mainly in the lung, but also in the kidney and brain, to an octapeptide, angiotensin II, which is a potent vasoconstrictor and also stimulates the release of aldosterone. Aldosterone is an adrenal cortex hormone that promotes the retention of salt and water by the kidneys and thus increases plasma volume, resulting in an increase in blood pressure. Angiotensin II also stimulates the release of norepinephrine from neural cells which interacts with specific receptors on blood vessels, thereby resulting in an increase in calcium and vasocontriction. Another mechanism by which angiotensin II induces vasoconstriction is by interacting with specific receptors on blood vessels, thereby resulting in an opening of calcium channels and an increase in calcium, resulting in vasoconstriction.

ACE, also referred to as peptidyl dipeptidase A (EC 3.4.15.1) and kininase II is a metallopeptidase, more particularly a zinc peptidase which hydrolyses angiotensin I and other biologically active polypeptides, such as kinins, e.g., bradykinin. Bradykinin is a vasodilator, which acts at least in part by inducing release of vasodilator prostaglandins,

and which is inactivated upon hydrolysis by ACE. Thus, ACE increases blood pressure at least in part by producing angiotensin II, a vasoconstrictor, and by inactivating bradykinin, a vasodilator. Bradykinin is also involved in other biological activities including mediation of pain and inflammatory reactions.

The role of ACE in regulating blood pressure is further demonstrated at least by the efficacy of ACE inhibitors in reducing hypertension and treating CHF in individuals. ACE inhibitors have major roles as vasodilators in hypertension and CHF and are among the most efficient drugs for treating these disorders (see, e.g., Opie et al., Angiotensin Converting Enzyme Inhibitors and Conventional Vasodilators, in Lionel H. Opie, Drugs for the Heart, Third Edition, WB Saunders Company, 1991, p106). Several clinical trials indicate that ACE inhibitors prolong survival in a broad spectrum of patients with myocardial infarction and heart failure, ranging from those who are asymptomatic with ventricular dysfunction to those who have symptomatic heart failure but are normotensive and hemodynamically stable. For example, one study demonstrated a 40% reduction in mortality at 6 months in patients with severe heart failure (The CONSENSUS Trial Study Group, *N. Engl. J. Med.* 316:1429 (1987); The CONSENSUS Trial Study Group, *N. Engl. J. Med.* 325:293 (1991)).

Several ACE inhibitors are currently available on the market (e.g., CAPTOPRIL, ENALAPRIL, FOSINOPRIL, LINSINOPRIL, and RAMIPRIL). However, ACE inhibitors in large doses can cause a variety of undesirable secondary effects including nephrotic syndrome, membraneous glomerulonephritis, nephritis, and leukopenia, as well as angioedema. Therefore, it would be advantageous to identify alternate therapies useful for treating blood pressure disorders, (e.g., hypertension) to avoid the side effects and improve the efficacy associated with the ACE inhibitors currently available.

Summary of Invention:

The invention pertains to, at least in part, compounds and methods for modulating the activity of ACE-2. In one embodiment, the invention features an ACE-2 inhibiting compound of the formula (I):

Z-L (I)

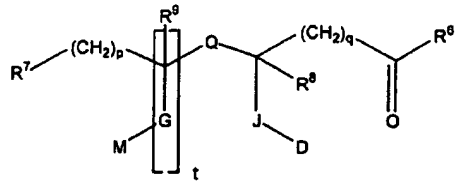
wherein Z is a zinc coordinating moiety, and L is an amino-acid mimicking moiety. In one embodiment, L is an amino acid mimic containing a non-polar side chain. In an advantageous embodiment, Z is a carboxylic acid or a cleavable prodrug moiety.

In another embodiment, the invention features an ACE-2 inhibiting compound of the formula (II):

Z-A-B-E **(II)**

wherein Z is a zinc coordinating moiety, E is an enzyme coordinating moiety, A is an auxiliary ACE-2 pocket binding moiety, and B is an ACE-2 side chain pocket binding moiety.

In another embodiment, the invention pertains to an ACE-2 inhibiting compound of the formula (III):



(III)

wherein R^6 is hydroxyl or a protecting prodrug moiety; R^7 is a carboxylic acid, arylaminocarboxy, aroyl, alkylaminocarboxy, aminocarboxy, alkenylaminocarboxy, , a protecting prodrug moiety, hydroxyl, heterocycle, alkoxy, ether, thiol or an amine; R^8 is hydrogen, or alkyl, and optionally linked to D to form a cyclic structure; R^9 is lower alkyl or hydrogen; Q is a bond, O, S, CHOH, CHSH, $CHNH_2$, $CHNHR^3$, $CHNR^3R^4$, NH, NR^3, $(CH_2)_n$, $O(CH_2)_n$, $(CH_2)_nO(CH_2)_n$, wherein n is either 0, 1, 2, or 3, and R^3 and R^4 are each independently substituted or unsubstituted C_1-C_5 branched or straight chain alkyl, C_2-C_5 branched or straight chain alkenyl, substituted or unsubstituted acyl, aryl, C_3-C_8 ring, optionally substituted with up to four heteroatoms; G is a linking moiety; M is an anchor moiety; J is a bond, an alkyl, alkenyl, or alkynyl moiety; D is hydrogen, alkyl, amine, hydroxy, alkenyl, alkynyl, aryl, or heteroaryl, optionally linked to G , M or Q to form a ring; t is 0, 1, 2, or 3; p is 0, 1, 2, 3, 4, or 5; q is 0, 1, 2, or 3.